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PATENT
Our Docket: P-LA 1245

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1644

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Border and Ruoslahti	Group Art Unit: 1644
Serial No: 08/349,479	Examiner: P. Gambel
Filed: December 2, 1994	
For: INHIBITING TRANSFORMING GROWTH FACTOR β TO PREVENT ACCUMULATION OF EXTRACELLULAR MATRIX	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Attention Box AF, Washington, D.C., 20231, on March 15, 2001.

By _____
Robert T. Ramos, Reg. No. 37,915

March 15, 2001
Date of Signature

Box AF
Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION

Responsive to the Office Action mailed September 15, 2000, Applicants respectfully request consideration of the following remarks.

REMARKS

Claims 21 to 23 and 25 are presently under examination. The invention, as defined by independent claim 21, is directed to a method of decreasing the deleterious accumulation of extracellular matrix (ECM) associated with a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue by contacting the tissue with an anti-TGF-β antibody that binds to TGF-β; whereby the binding of the anti-TGF-β antibody to the TGF-

β suppresses the deleterious accumulation of the TGF-β-induced extracellular matrix in the tissue. Dependent claims 22, 23 and 25 are directed to the method of claim 21 and further recite specific pathologies or conditions.

Rejection under 35 U.S.C. §102(e)

The rejection of claims 21, 23 and 25 under 35 U.S.C. § 102(e) as allegedly anticipated by Dasch et al., United States Patent No. 5,772,998, respectfully, is traversed.

Applicants respectfully submit that, in deciding the sufficiency a Rule 131 Declaration, the Examiner is bound by the framework provided by the controlling law, which is consistent with MPEP § 715.07. As acknowledged by the Examiner on page 3, paragraph 8, of the current Office Action, the law does not require Applicants to provide exhibits supporting every limitation of the claims. In this regard, the MPEP states that evidence in the form of exhibits may accompany the declaration, but does not require such extrinsic evidence (see MPEP §715.07). Moreover, in Ex Parte Ovshinsky, 10 USPQ2d 1075 (Bd. Pat. App. & Inter. 1989) the court indicates at page 1077:

> We point out to the Examiner that (1) all the evidence must be considered in its entirety, including the Rule 131 declarations and accompanying exhibits, records and 'notes,' (2) an accompanying exhibit need not support all of the claimed limitations but rather a missing feature may be supplied by

> the Declaration itself, and (3) it is entirely appropriate for appellants to rely on a showing of facts set forth in the Rule 131 declarations themselves to establish conception of the invention prior to the effective date of the reference. [citation omitted]

As set forth by the Ovshinsky Court, there is no requirement to produce additional exhibits as Applicants' reliance on the showing of facts set forth in the Rule 131 declaration itself is entirely appropriate to establish conception of the invention prior to the effective date of the reference.

Applicants respectfully submit that conformity with the Swaney fact pattern has not been articulated by any court in the country, including the Swaney Court itself, as the test for sufficiency of a Rule 131 Declaration. With regard to the Examiner's discussion of the factual circumstances underlying the Ex parte Swaney decision, the Examiner argues that in Swaney the missing element had apparently been performed in the experiments described in appellants exhibits and that there merely was a lack of mention of the performance of the missing element in the exhibits themselves (current Office Action, Paper No. 67, page 3, paragraph 9). This statement as well as the following paragraph of the current Office Action appears to suggest that the Swaney facts represent the controlling legal standard for sufficiency of a Rule 131 Declaration. However, no court has held that in order to show conception prior to a critical date, Applicants have to

provide exhibits that explicitly or implicitly contain all elements of the claimed invention.

As set forth above, under the controlling legal standard articulated by the Ovshinsky Court "it is entirely appropriate for appellants to rely on a showing of facts set forth in the Rule 131 declarations themselves to establish conception of the invention prior to the effective date of the reference."

Applicants herewith submit as Exhibit 1, a new Rule 131 Declaration executed by Drs. Border and Ruoslahti and respectfully request that the Examiner apply the controlling case law to the facts averred to by Applicants in their Rule 131 Declaration. In their Rule 131 Declaration, Drs. Border and Ruoslahti aver that they conceived, prior to December 22, 1988, the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring, by contacting the affected tissue with an anti-TGF-β antibody. Furthermore, Drs. Border and Ruoslahti aver that they diligently pursued, and conducted all experiments and work related to, the claimed invention in the United States starting prior to December 22, 1988, until the filing date of the priority application.

Applicants provide corroborating exhibits A through E along with their Rule 131 Declaration. Each of the corroborating exhibits relates either to the conception of the claimed methods prior to December 22, 1988, or to Applicants due diligence in pursuing reduction to practice of the claimed methods during the critical period. The critical period in which diligence must be shown begins just prior to the effective date of the reference and ends with the date of a reduction to practice, either actual or constructive. Furthermore, the filing of a United States patent application represents constructive reduction to practice.

Applicants respectfully submit that the Rule 131 Declaration and accompanying Exhibits A through E, which are addressed in turn below, establish Applicants conception of the claimed methods prior to December 22, 1988, as well as Applicants diligence in the pursuit of reducing to practice the claimed methods from prior to December 22, 1988, until the filing of the priority application.

In their Rule 131 Declaration, Drs. Border and Ruoslahti aver that they conceived, prior to December 22, 1988, the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition by contacting the affected tissue with an anti-TGF-β antibody. This averment is supported by the Declaration under Rule 132 by Lucia Languino, Ph.D., which is attached as Exhibit A to Applicants' Rule 131 Declaration as well as independently attached as Exhibit 2 to this Response.

In her Rule 132 Declaration Dr. Languino avers that she was a postdoctoral fellow in Dr. Ruoslahti's laboratory during the time period Dr. Border conducted research related to the above-identified patent application in the same laboratory. Dr. Languino further avers that, prior to December 22, 1988, Drs. Border and Ruoslahti asked her to assist in the preparation of anti-TGF-β antibodies for a stated goal of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease. Attached as Exhibit A to Dr. Languino's Declaration is a La Jolla Cancer Research Foundation "Animal Usage Form," the redacted date of which is prior to December 22, 1988, related to the project entitled "Anti-human TGF-β Cyclic Peptide," which lists Drs. Border and Languino as the investigators. Thus, Dr. Languino corroborates, based on personal observations, that Applicants, prior to December 22, 1988, conceived of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease. Therefore, Exhibit A provides an independent third party corroboration by Dr. Languino with regard to the facts averred to by Applicants in their Rule 131 Declaration.

Exhibit B to Applicants Rule 131 Declaration consists of two laboratory notebook pages from Dr. Languino's notebook that show the protocol for development of a rabbit anti-TGF-β antiserum substantially as set forth in Example III.e of Applicants' specification, and a La Jolla Cancer Research

Foundation "Animal Procedure Request" form. The laboratory notebook pages from Dr. Languino's notebook have a redacted date prior to December 22, 1988, and set forth protocols for injection of rabbits with TGF-β peptides, including linear and cyclic TGF-β peptides, in order to prepare anti-TGF-β antiserum. The La Jolla Cancer Research Foundation "Animal Procedure Request" form in Exhibit B of the Rule 131 Declaration lists Drs. Ruoslahti and Languino as principal investigators and indicates the dates on which the animals were bled for anti-TGF-β serum, December 13, 16 and 21 of 1988.

As set forth above, Dr. Languino assisted Applicants in the preparation of anti-TGF-β antibodies for a stated goal of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease. The handwritten notations on the notebook page to which the "Animal Procedure Request" form is attached in Exhibit B are Dr. Languino's notations indicating that the rabbits were injected with Proteoglycan 1 (PG1), TGF-β linear peptide and TGF-β cyclized peptide. Applicants aver in their Rule 131 Declaration that, at time the documents encompassed in Exhibit B were created, a stated goal of preparing anti-TGF-β antibodies was for their use to inhibit TGF-β in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a pathology or condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring.

Further corroboration of Applicants conception of the claimed methods prior to December 22, 1988, is provided by Exhibit C to the Rule 131 Declaration, a conference abstract published for the Meeting of the American Society of Nephrology in San Antonio, Texas, which took place from December 11 to 14, 1988. This conference abstract, which lists Drs. Border and Ruoslahti as first and senior authors, respectively, is entitled "Transforming Growth Factor β (TGFβ) Uniquely Regulates Production of Glomerular Extracellular Matrix" and is consistent Applicants' conception of treating pathologies related to TGFβ-mediated accumulation of extracellular matrix prior to December 22, 1988. In particular, the abstract provides evidence that Drs. Border and Ruoslahti discovered that TGFβ is unique among growth factors in its ability to stimulate ECM production, which is increased in glomerulonephritis. In this regard, Drs. Border and Ruoslahti declare in their Rule 131 Declaration that at the time this abstract was submitted, they already had conceived of using anti-TGF-β antibodies in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with glomerulonephritis or other pathologies associated with TGF-β-induced expansion of the ECM.

Exhibit D to the Applicants' Rule 131 Declaration speaks to Applicants' diligence in pursuing the reduction to practice of the claimed methods during the critical period. Specifically, Exhibit D consists of an excerpt from a grant application executed by Dr. Border in January of 1989 entitled "Growth Factors and Extracellular Matrix in Glomerular Disease." In the excerpt, the following goal is explicitly stated in the

section entitled Specific Aims, *In vivo*:

> To develop regimens for therapeutic intervention in the disease model by antibodies and other agents capable of neutralizing the TGFβ effect.

In addition, the section related to Experimental Design and Methods, explicitly states:

> We have proposed several experiments that may provide agents that could block or ameliorate the action of TGFβ in the animal model of mesangial injury...It is conceivable that one or more of these agents could be administered to the animal and/or infused directly into the kidney as therapeutic agents to prevent the expansion of mesangial matrix...We expect that one or more of the agents to be tested will block the action of TGFβ. This information would be immediately applicable to the design of a study to treat humans with glomerulonephritis.

Thus, it is respectfully submitted that Exhibit D, at a minimum, corroborates Applicants' averments that the reduction to practice of the claimed therapeutic methods were being diligently pursued from prior to December 22, 1988, until the filing of the priority application. In addition, the content and purpose of the entire grant proposal, which includes a detailed description of Applicants' goals that are supported by extensive preliminary

data, is consistent with Applicants' averments in the attached Rule 131 Declaration of conception prior to December 22, 1988.

Further with regard to Applicants' diligence during the critical time period, submitted as Exhibit E to the Rule 131 Declaration documents are excerpts of an updated draft manuscript as it existed in August of 1989. The manuscript is entitled "An Antiserum Against Transforming Growth Factor β Suppresses Experimental Glomerulonephritis" and contains the *in vivo* protocol corresponding to Example VII of the specification, directed to treatment of anti-Thy-1-induced nephritic rats with control rabbit serum or anti-TGF-β serum. In the manuscript it is stated that the results achieved in experimental disease with anti-TGF-β treatment warrant the expectation of similar benefits for treatment of human glomerulonephritis and other fibrosis-related diseases. Applicants respectfully submit that Exhibit E provides documentation that during the critical period Applicants were diligently pursuing the reduction to practice of the claimed methods.

Overall, it is respectfully submitted that each element of Applicants claims is supported in the entirety of the corroborating exhibits Applicants have provided and the inventor's averments set forth in the attached Rule 131 Declaration. When viewed in its entirety, the evidence provided by Applicants' Rule 131 Declaration and accompanying Exhibits A-E, including the Rule 132 Declaration by Lucia Languino, Ph.D., shows Applicants conception of the claimed methods prior to December 22, 1988, as well as their diligent pursuit of the

claimed methods from prior to December 22, 1988, until the filing date of priority application. Accordingly, the Dasch et al. '998 patent has been antedated and cannot be used as prior art. Accordingly, reconsideration and withdrawal of the rejection respectfully is requested.

Rejections under 35 U.S.C. §103(a)

The rejection of claims 21 and 22 under 35 U.S.C. §103(a) as allegedly unpatentable over Dasch et al., supra, in view of Ruoslahti et al. (U.S. Patent 5,583,103) and/or Bassols et al., J. Biol. Chem., 263:3039-3045 (1988) is respectfully traversed.

Applicants respectfully submit that Applicants may overcome a 35 U.S.C § 103 rejection based on a combination of references by showing completion of the invention prior to the effective date of any of the references. Furthermore, Applicants need not antedate the reference with the earliest filing date. Applicants respectfully submit that in light of the arguments set forth above in response to the §102(e) rejection over Dasch et al., and the Rule 131 Declaration submitted herewith, the Dasch et al. '998 patent has been antedated and cannot be used as prior art. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he/she is invited to call Cathryn Campbell or the undersigned attorney.

Respectfully submitted,

March 15, 2001
Date

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Attachments:
Exhibit 1 - Rule 131 Declaration of Drs. Border and Ruoslahti
Exhibit 2 - Rule 132 Declaration of Dr. Lucia L. Languino